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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,072	01/25/2002	Genoveffa Franchini	15280-4003US	1664

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,072	FRANCHINI ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11252005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 25 November, 2005, has been entered.

Status of the Claims

New claim 18 accompanied the aforementioned response. Claims 1-3, 5-10, and 12-18 are currently under examination.

Claim Objections

The previous objection to claims 1-3, 5-10, and 12-17 because due to informalities is hereby withdrawn in response to applicants' amendment.

35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5-10, and 12-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out

and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Claim 1 references a "protective $CD8^+$ HIV **structural antigen** response" by administering a recombinant virus encoding both HIV-1 structural and non-structural gene products. For instance, the *nef* gene encodes a regulatory protein, not a structural protein. Thus, administration of a recombinant virus encoding this protein would not be expected to generate an HIV-1 structural antigen CTL response, but rather, an HIV-1 non-structural/regulatory antigen response. Appropriate correction, as supported by the disclosure, is required.

Concerning claim 18, the reference to a method that reduces the viral load in an immunodeficiency virus-infected individual is confusing. First, the recombinant virus is being administered to patients that already have a reduced viral load because of previous antiviral treatment. Thus, it is not readily manifest if the claims are really directed toward reductions in viral load, the maintenance of low viral loads, or the prevention of rebounding viral loads after the cessation of antiviral administration or because of the development of drug-resistant variants. Second, the claims involve the administration of a recombinant virus that induces a "protective $CD8^+$" HIV-specific immune response. Thus, it is not readily manifest if the claims are actually directed toward the generation of an HIV-1-specific CTL response or a method of lowering the viral burden. Appropriate clarification and correction are required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 5-10, and 12-18 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods of inducing a protective HIV-1-specific $CD8^+$ immune response in an infected individual by administering a recombinant virus encoding HIV-1 structural proteins (e.g., Gag, Pol, or Env) or a non-structural protein (e.g., Nef). Additonal claim stipulations require the composition to be administered to patients with viral loads <10,000 copies per ml of plasma and $CD4^+$ cell counts >500 cells/ml. The claims also encompass reductions in viral load by administering compounds that induce protective HIV-1-specific CTL responses.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the

prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the correlates of human protection. To date, it is not clear what type of immune response is required to provide a therapeutic benefit. If a $CD8^+$ T-cell response is protective or therapeutic, what is the specificity of the immune response (i.e., which CTL epitopes are responsible for protection?), what is the titer of $CD8^+$ T-cells that are required for protection, and what duration is required to maintain protection? The disclosure fails to adequately address these concerns. Applicants traverse and submit that the claims are clearly directed toward an increased $CD8^+$ T-cell response that is responsible for protection. It was also argued that the titer is not necessarily a good indicator of the CTL response. These arguments are not deemed to be persuasive. The only data relied upon was generated in the macaque model which is not reasonably predictive of human efficacy (Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al.*, 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995). Moreover, contrary to applicants' assertion, Altes *et al.* (2002) suggest the specificity, magnitude, and duration of the immune response (IR) are critical.

2) HIV vaccines frequently fail because of the *quasispecies* nature of HIV infection. The plasticity of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. HIV-1 exists as a large pool of genotypically and phenotypically distinct

isolates. It has been well-documented that the virus relies upon this heterogeneity to escape immune surveillance and detection. For instance, the majority of the neutralizing antibody response is directed toward a molecular determinant (V3) that undergoes rapid mutation. Thus, even when a neutralizing antibody or $CD8^+$ response is generated, it rapidly becomes ineffective as other members of the *quasispecies* quickly replicate and grow out. The disclosure fails to provide any data addressing this concern.

3) The disclosure fails to provide sufficient guidance pertaining to those immunogens that are capable of conferring protection. The claims are broadly directed toward any recombinant viral vaccine encoding a peptides obtained from the Gag, Pol, Env, or Nef proteins. However, the disclosure fails to provide any guidance pertaining to the molecular determinants modulating protective immune responses. Which CTL epitopes are capable of stimulating a protective or therapeutic immune response of the proper specificity, titer, and duration? Applicants argue that they need not describe every nuance of the claimed invention. This argument is clearly not persuasive. In order to generate a protective or therapeutic $CD8^+$ IR in an infected patient, it would be quite useful for the skilled artisan to know the CTL epitopes that are responsible for the protective or therapeutic effect. This would enable the skilled artisan to tailor the immunogen to contain these epitopes.

4) The disclosure fails to provide any working embodiments. The only human example is purely prophetic and fails to set forth any meaningful data. Some data was provided from the macaque model, however, this model is not an art-recognized model for vaccine development. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such

studies cannot be directly extrapolated to a clinical setting due to the structural differences between SIV and HIV. Applicants submit that previous declaratory statements and art provide working embodiments. First, applicants are reminded that the claims are broadly directed toward any recombinant virus encoding Gag, Pol, Env, and Nef. The declaration of Dr. Franchini references a study employing a single construct which is insufficient to support the full breadth of the claimed invention. Second, contrary to applicants' assertion, the macaque model is not reasonably predictive of the clinical efficacy (Haynes *et al.*, 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al.*, 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995).

5) The state-of-the-art vis-à-vis HIV CTL vaccine development is one of unpredictability (Haynes *et al.*, 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al.*, 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995). Contrary to applicants' assertions, to date, there is not one single effective HIV CTL vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response. Common problems encountered with vaccine development include the extraordinary variability, or *quasispecies* nature of HIV, the lack of an exact animal model of HIV-induced AIDS, and the lack of understanding of the correlates of protective immunity. The disclosure fails to address these concerns. Moreover, applicants are reminded that enablement is determined as of the effective filing date of the application (28 July, 1999). *Chiron Corp.* v. *Genentech Inc.*,

363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325-26 (Fed. Cir. 2004). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402,405-06 (C.C.P.A. 1976); *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

20 February, 2006